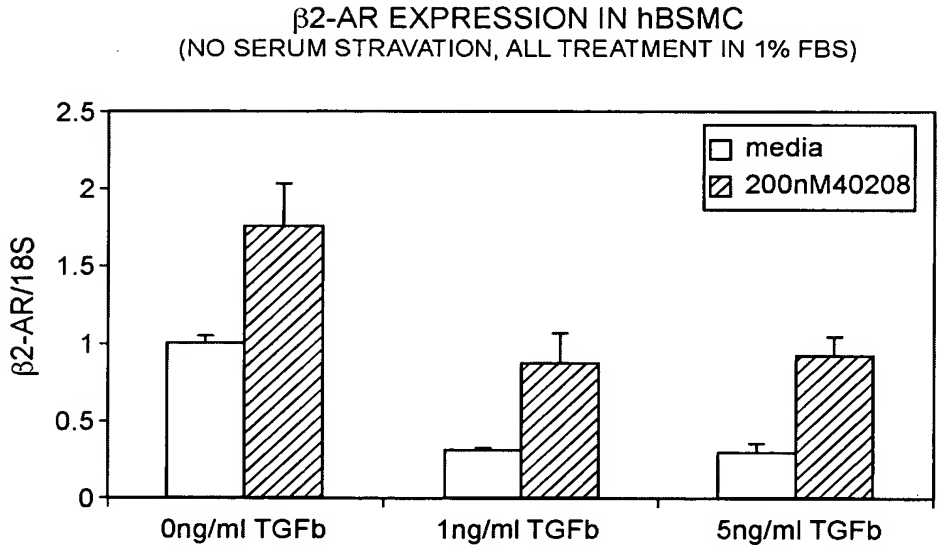
FIG. 1

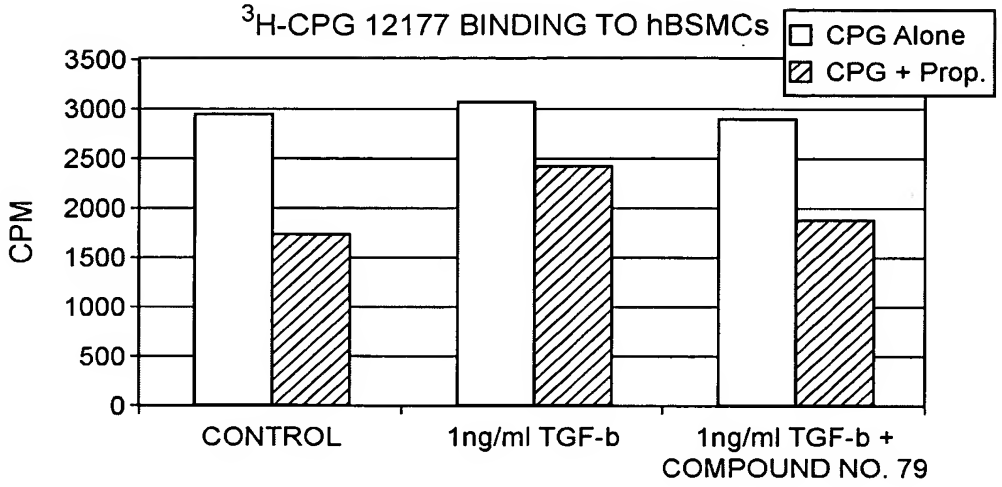
TGF-β1 EXPOSURE REDUCES β2-AR mRNA
IN HUMAN BRONCHIAL SMOOTH MUSCLE CELLS



*β1-AR mRNA IS UNDETECTABLE IN hBSMC

FIG. 2

TGFβ EXPOSURE REDUCES βAR BINDING SITES ON hBSMC



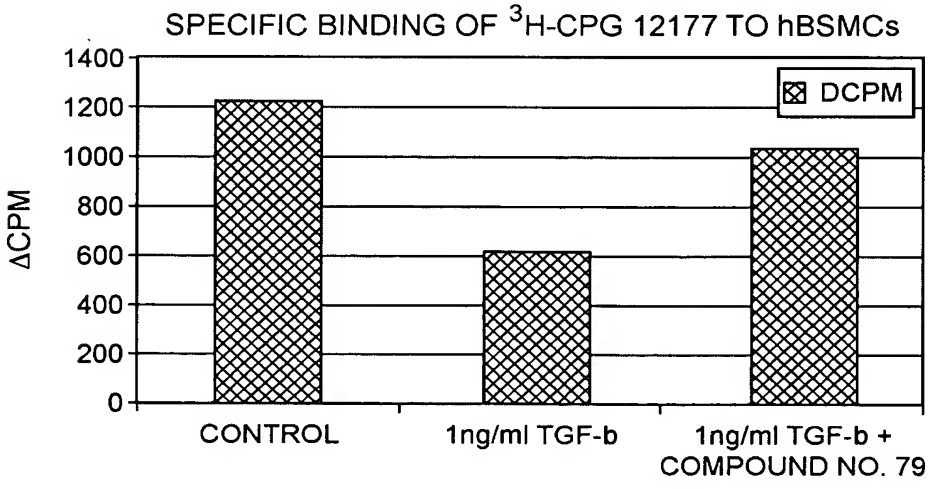
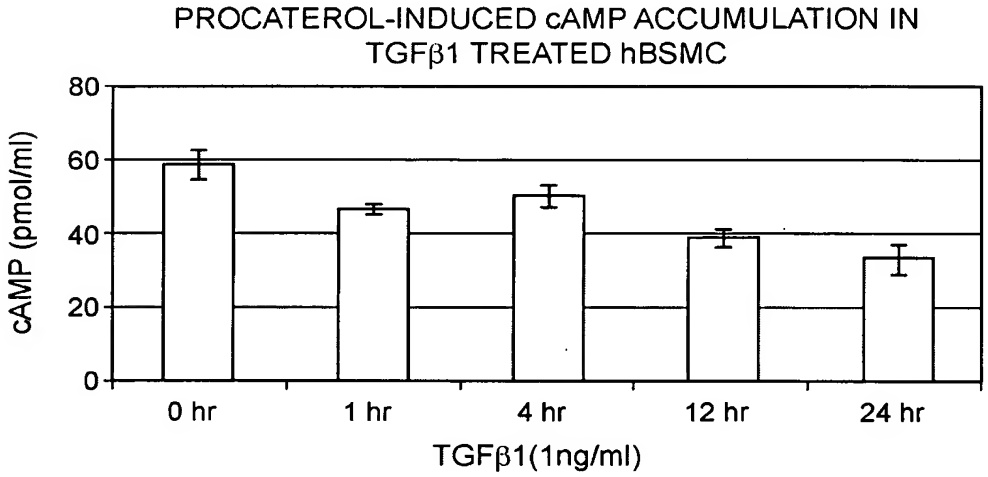
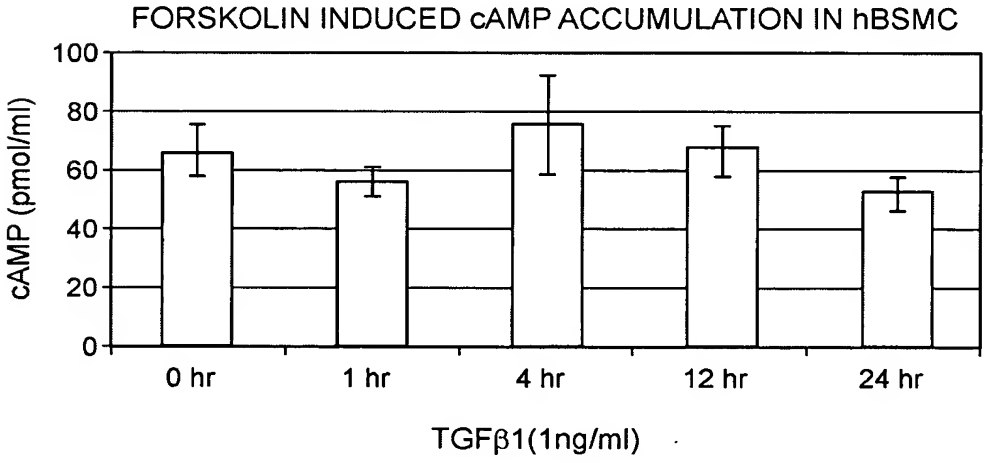


FIG. 3

TGFβ INDUCES Smad2 PHOSPHORYLATION AND REGULATES β2-AR/AC SIGNALING IN hBSMC





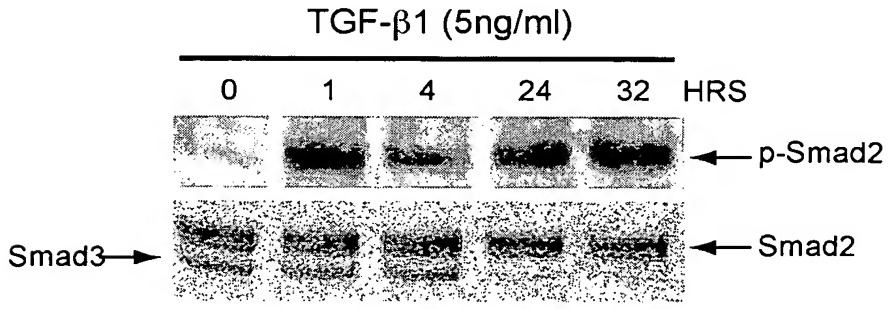
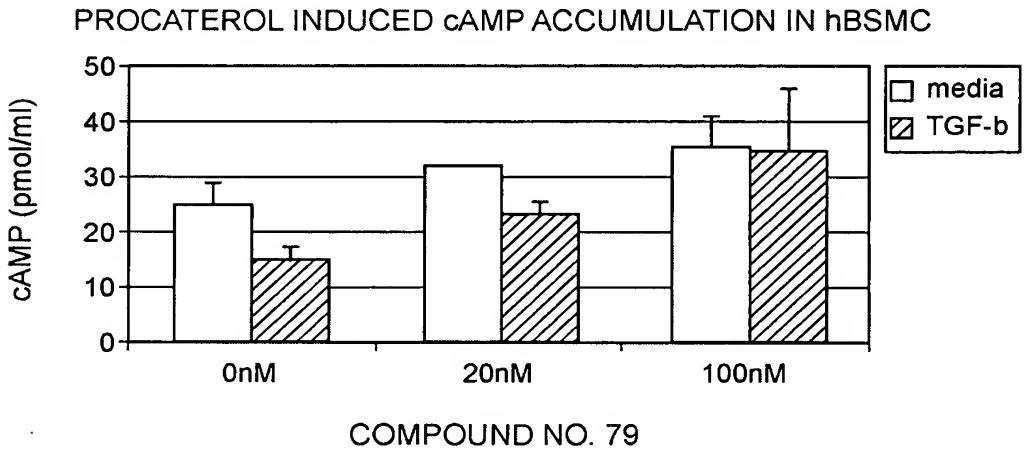
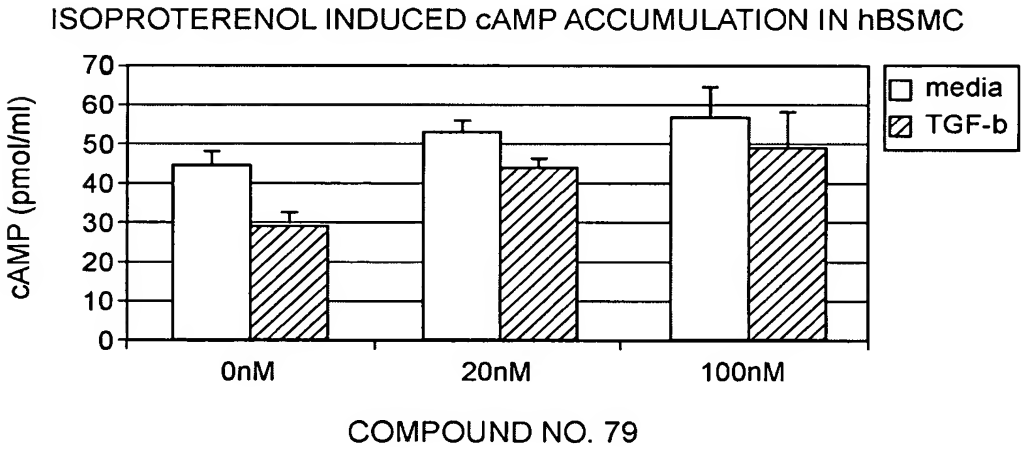


FIG. 4

TGFβ-RI KINASE INHIBITORS PREVENT TGFβ INDUCED LOSS OF ADRENERGIC RESPONSIVENESS IN hBSMC





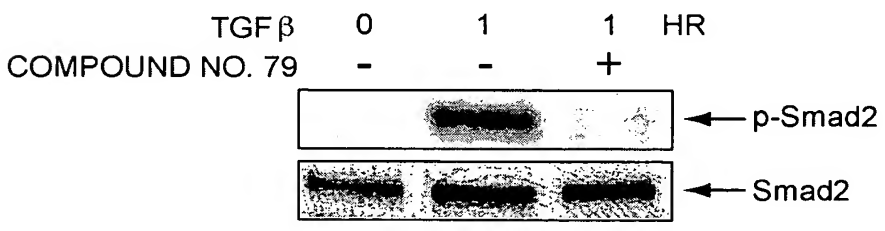
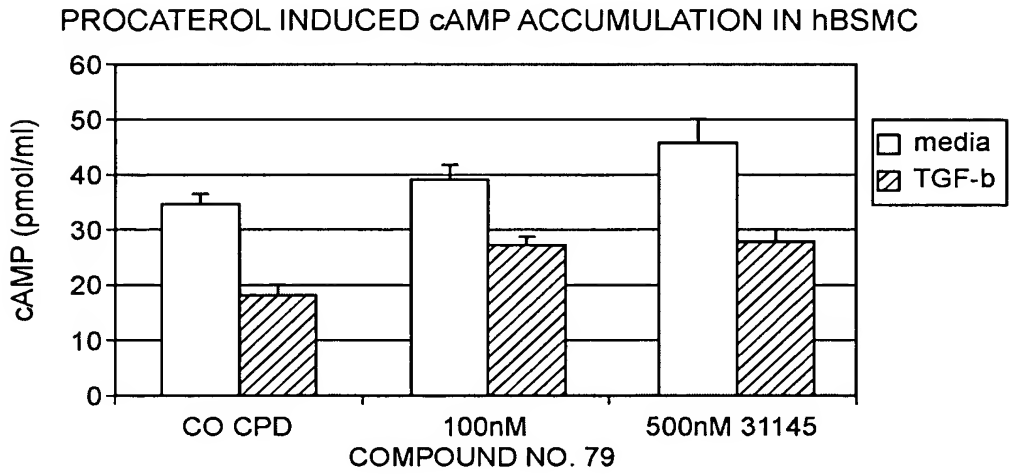
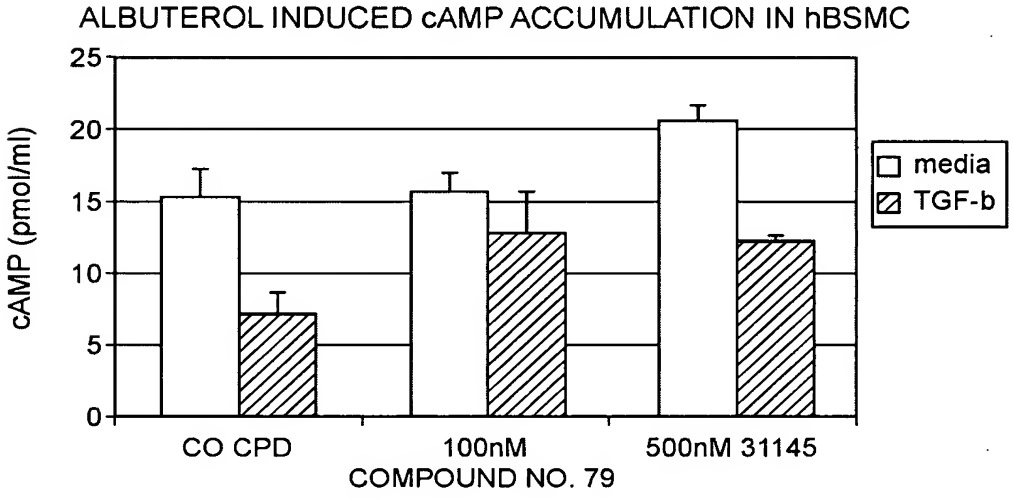


FIG. 5

IS p38 KINASE ALSO INVOLVED IN TGFβ REGULATED β-AR SIGNALING IN hBSMC?





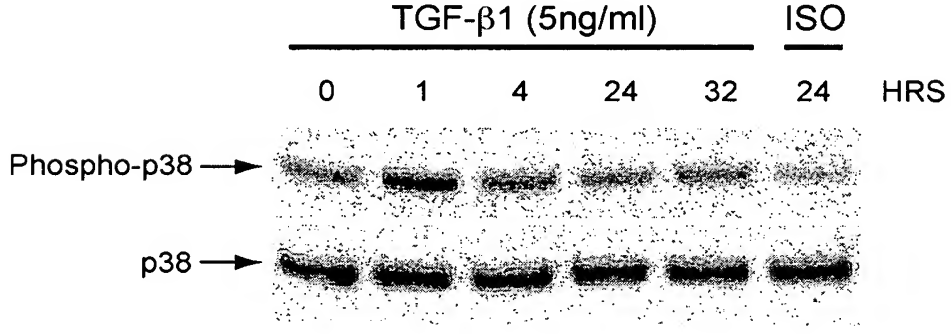


FIG. 6

ACTIVIN INDUCED LOSS OF βAR RESPONSE/AC SIGNALING IS ALSO REVERSED BY TGFβ RI INHIBITOR IN hBSMC

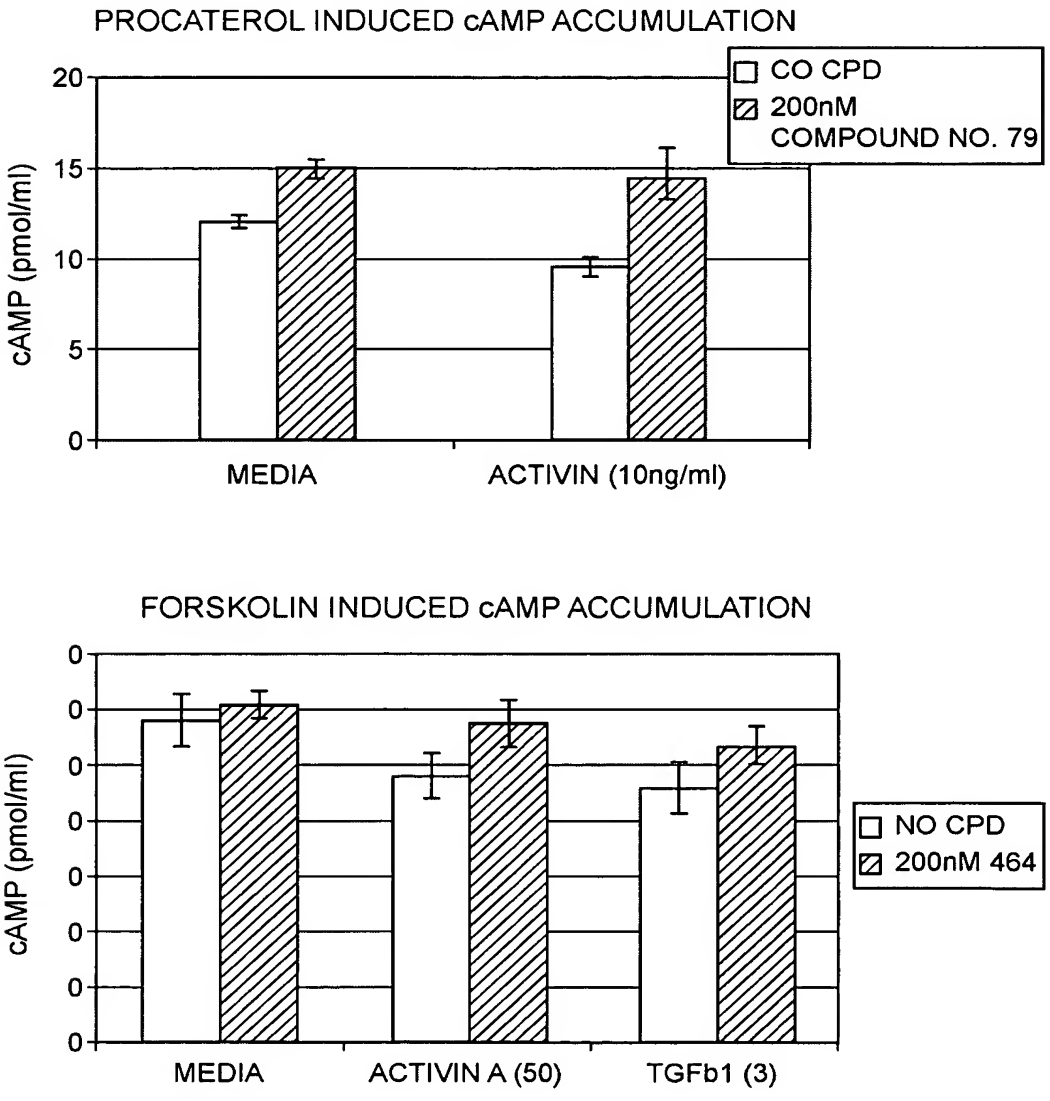


FIG. 7

TGFβ DOWN-REGULATES β2-AR mRNA IN RAT NEONATAL CARDIOMYOCYTES

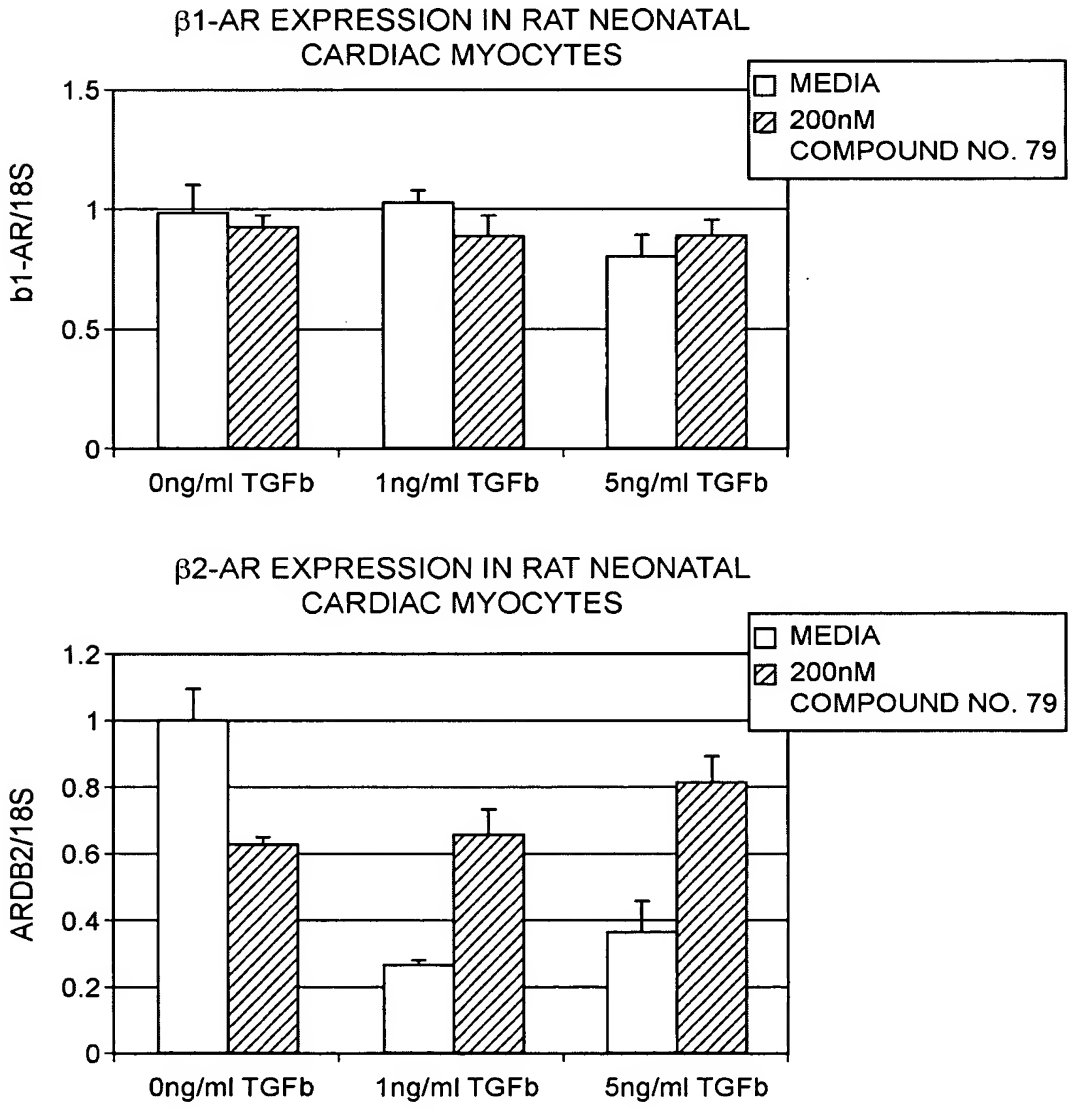
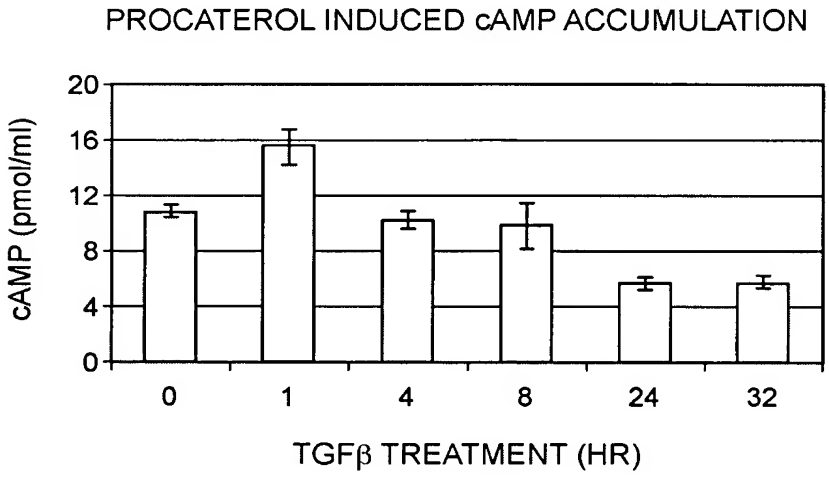


FIG. 8

TGFβ INDUCES Smad2 PHOSPHORYLATION AND CAUSES LOSS OF β2-AR RESPONSE IN RAT CARDIOMYOCYTES



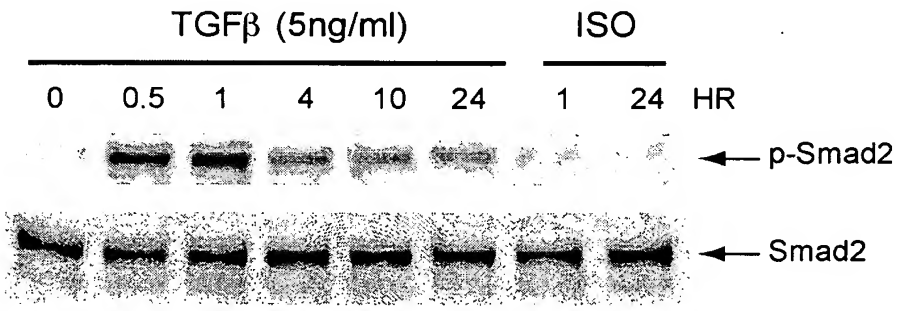


FIG. 9

COMPOUND NO. 79 PREVENTS TGFβ -INDUCED LOSS OF β2-AR RESPONSE/AC ACTIVITY IN RAT NEONATAL CARDIOMYOCYTES

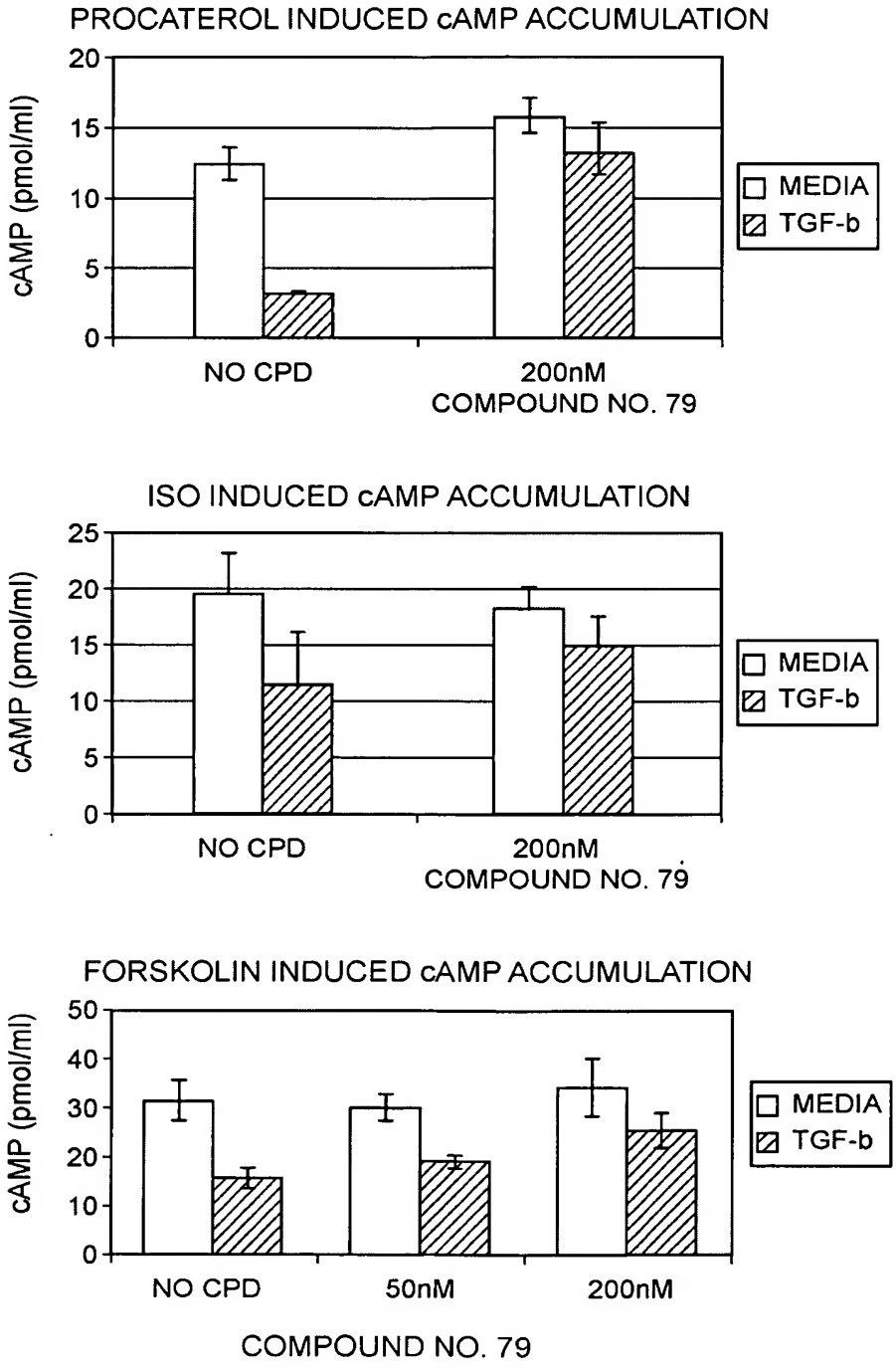
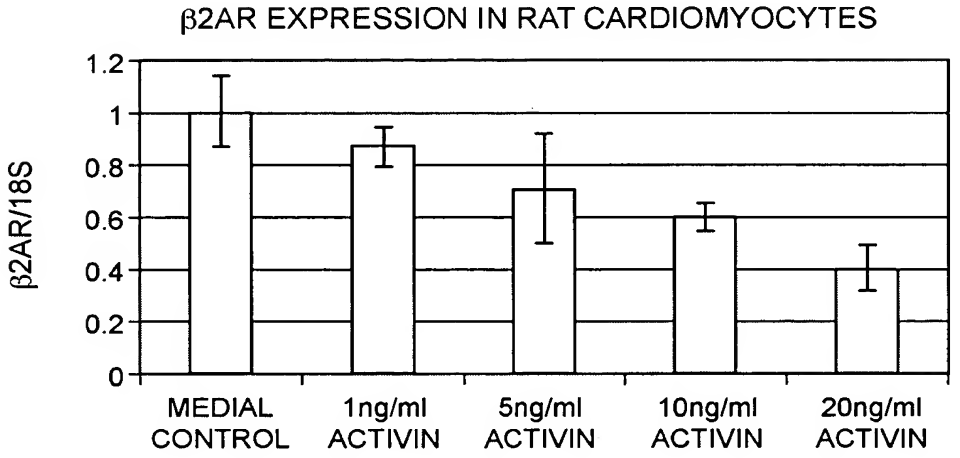
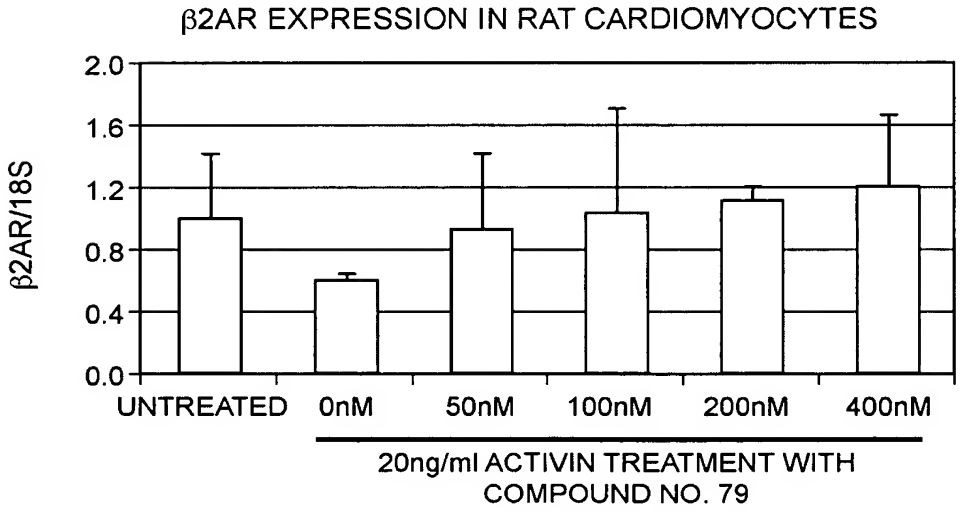


FIG. 10

ACTIVIN REDUSES β2-AR mRNA IN RAT NEONATAL CARDIOMYOCYTES

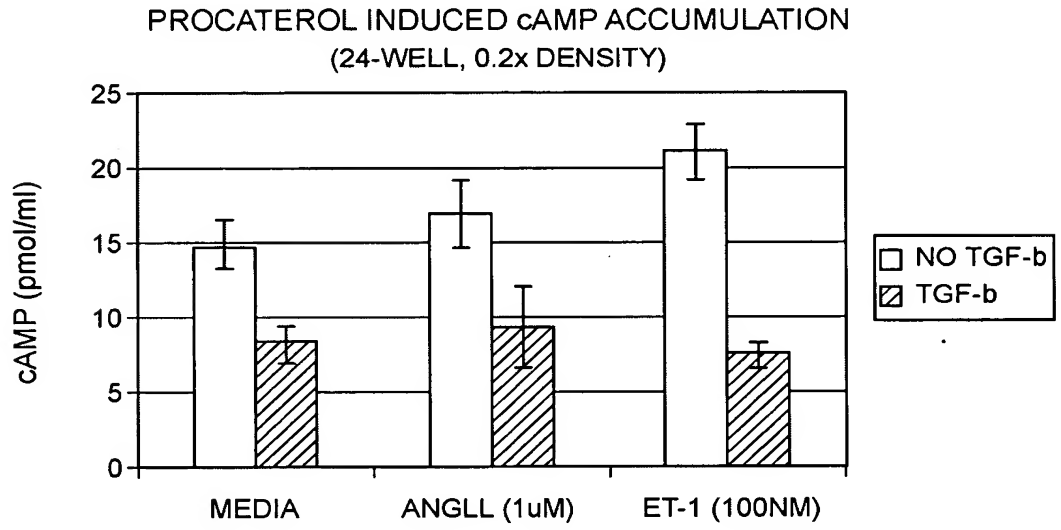




* TAQMAN ANALYSIS SHOWED NO EFFECT ON b1AR mRNA

FIG. 11

EFFECTS OF TGFβ AND HYPERTROPHIC STIMULI ON β2-AR SIGNALING IN RAT CARDIOMYOCYTES



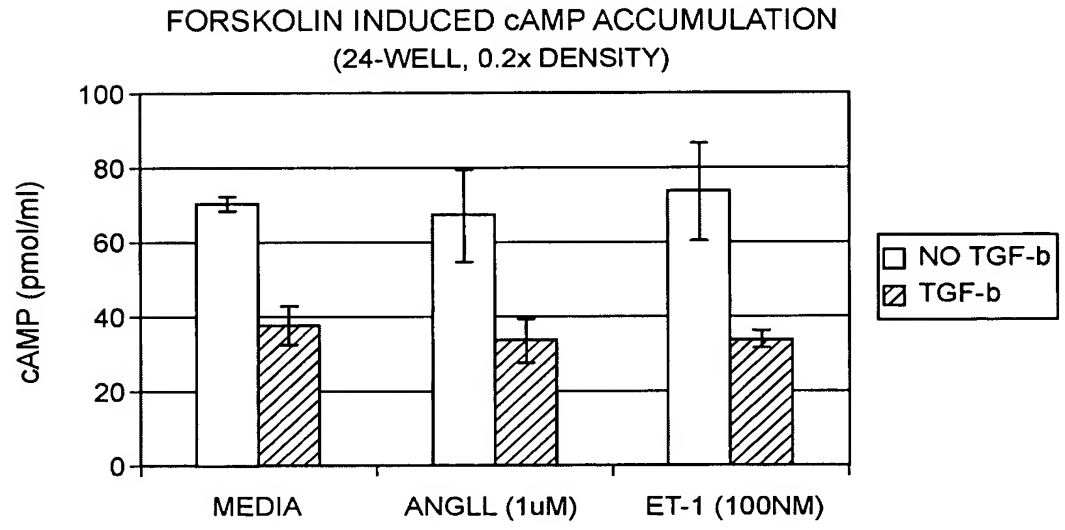
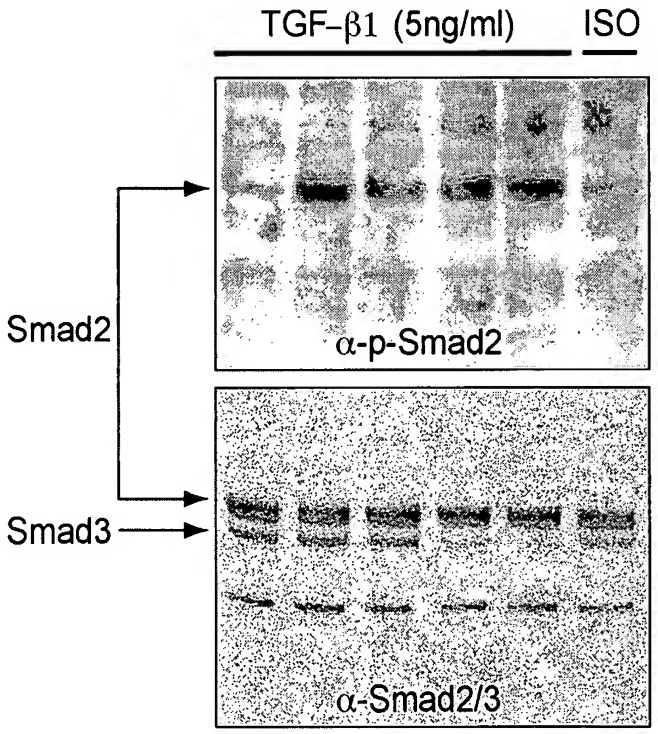
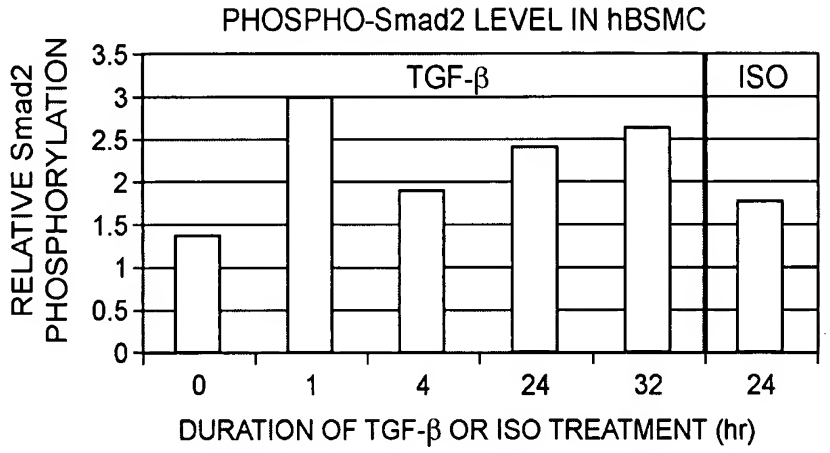


FIG. 12

TGFβ INDUCES Smad2 PHOSPHORYLATION AND DOWN-REGULATES Smad3 EXPRESSION IN hBSMC





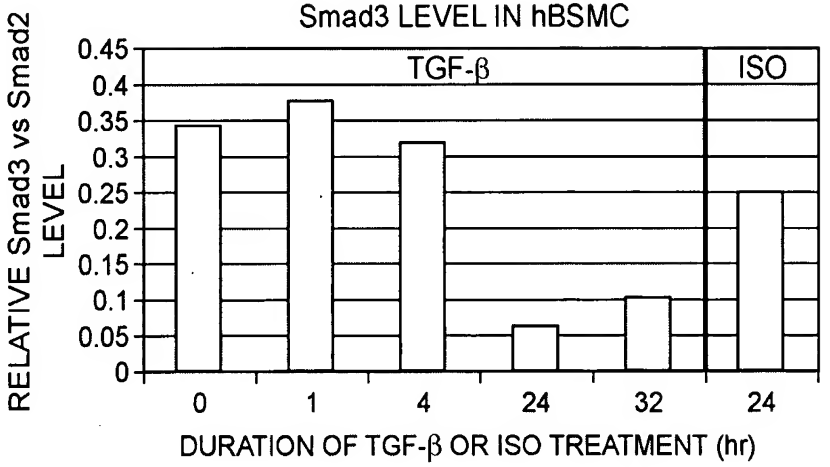


FIG. 13

COMPOUND NO. 79 BLOCKS TGFβ INDUCED Smad2 PHOSPHORYLATION AND Smad3 DOWN-REGULATION IN hBSMC

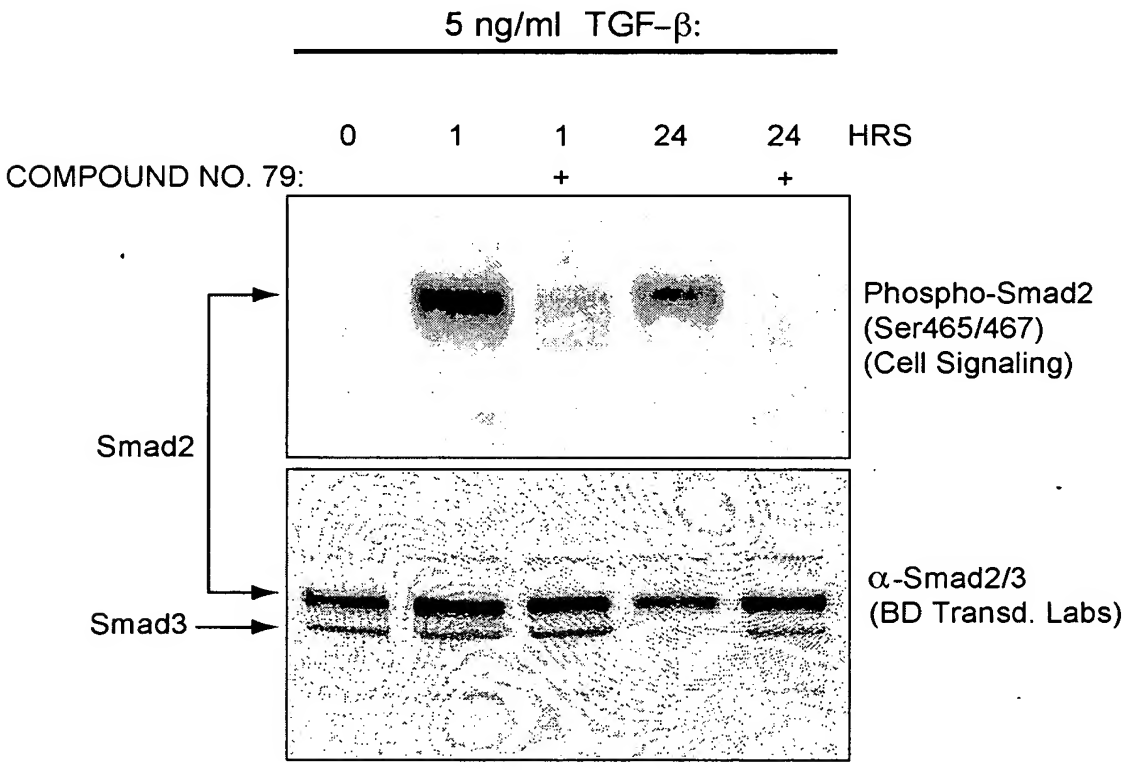
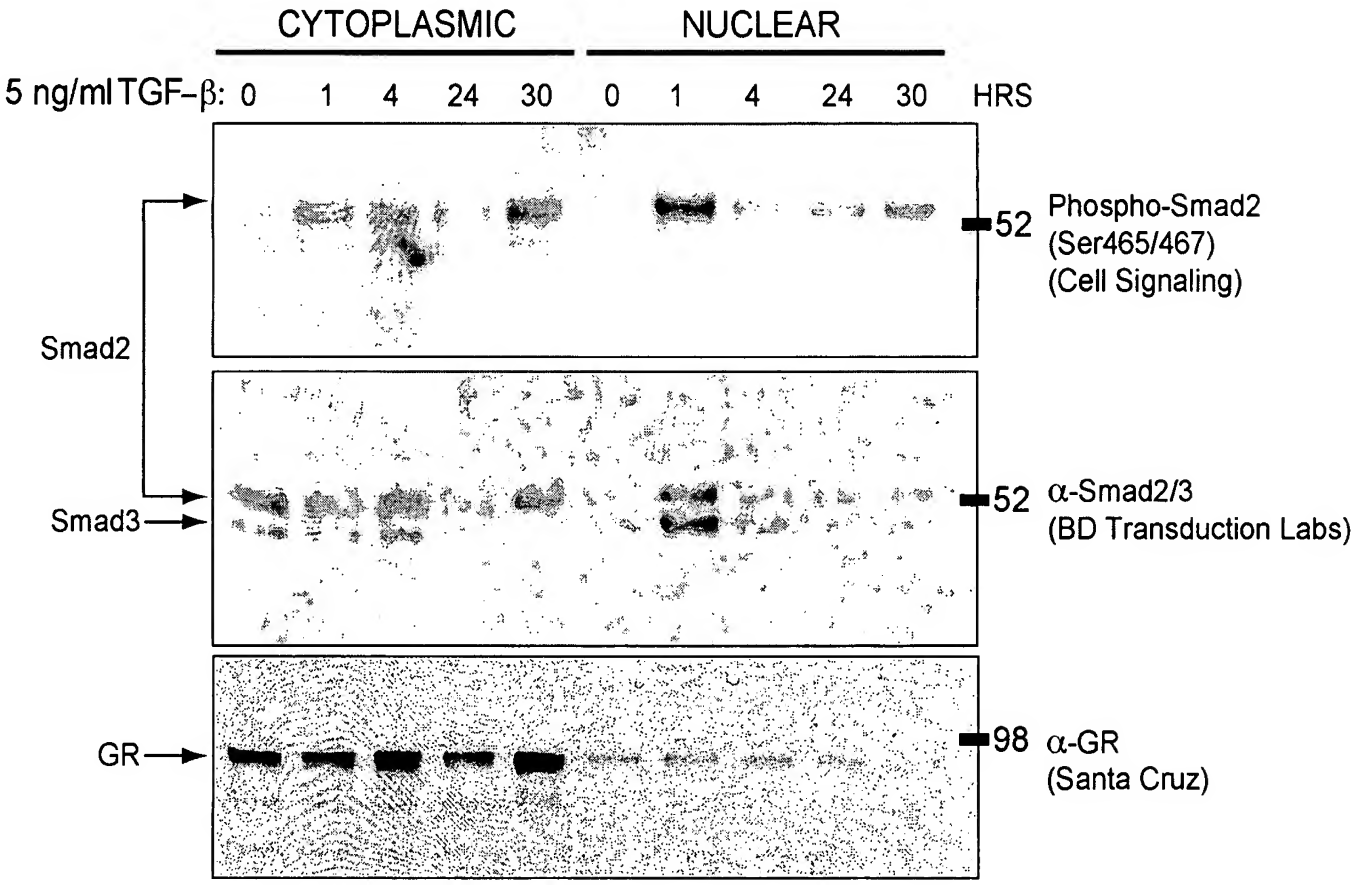


FIG. 14

TGFβ EXPOSURE INDUCES Smad2/3 TRANSIENT TRANSLOCATION INTO NUCLEUS IN hBSMC



- Glucocorticoid receptor (GR) is cytoplasmic steroid receptor translocating into nucleus in response to hormone stimulation

FIG. 15

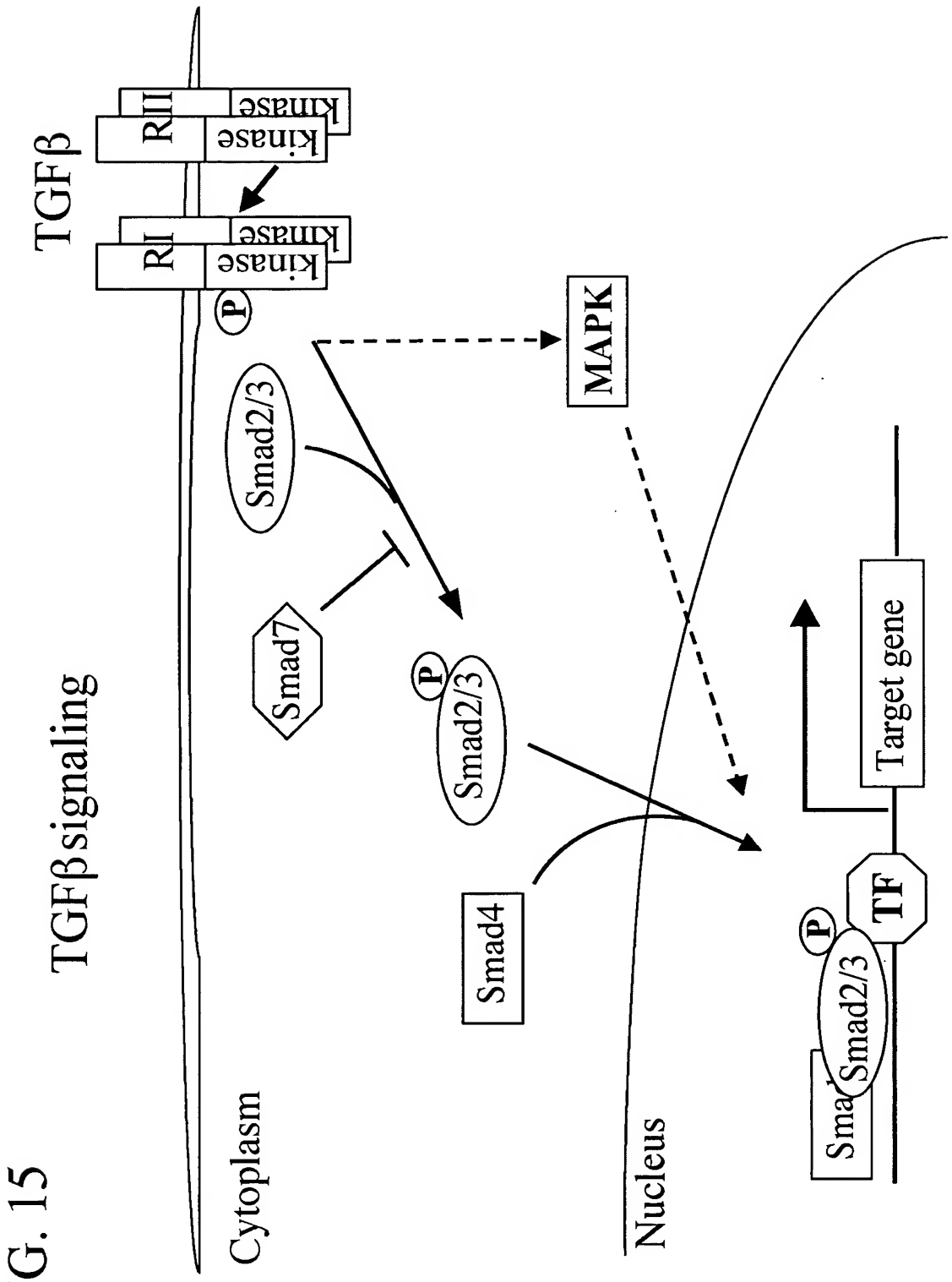

TGFβ signaling
TGFβ
RII
Kinase
Kinase
RI
Kinase
Kinase
P
Smad2/3
Smad7
MAPK
P
Smad2/3
Smad4
Target gene
TF
P
Smad2/3
Cytoplasm
Nucleus

FIG. 16

THE β-ADRENERGIC SIGNALING CASCADE

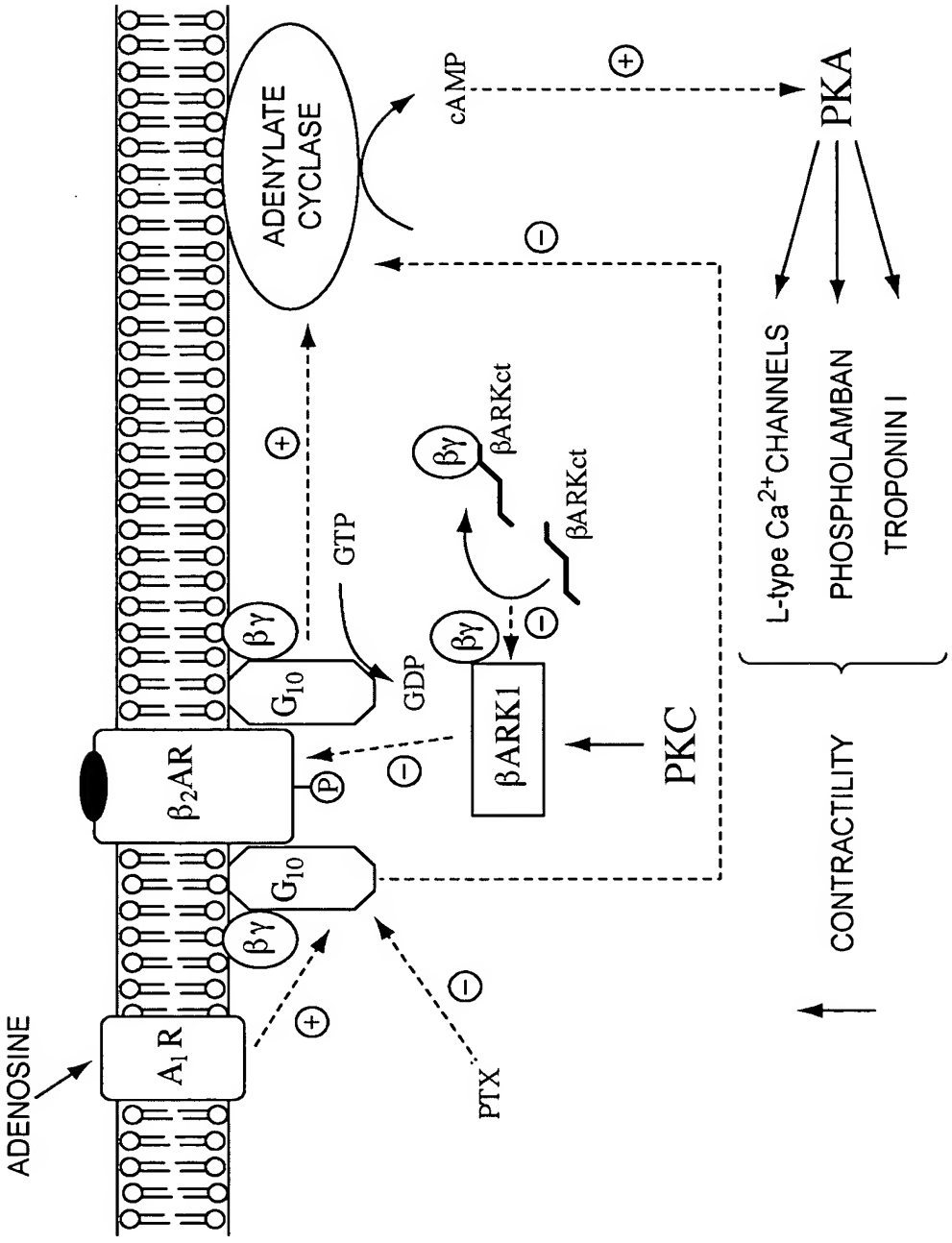


FIG. 17

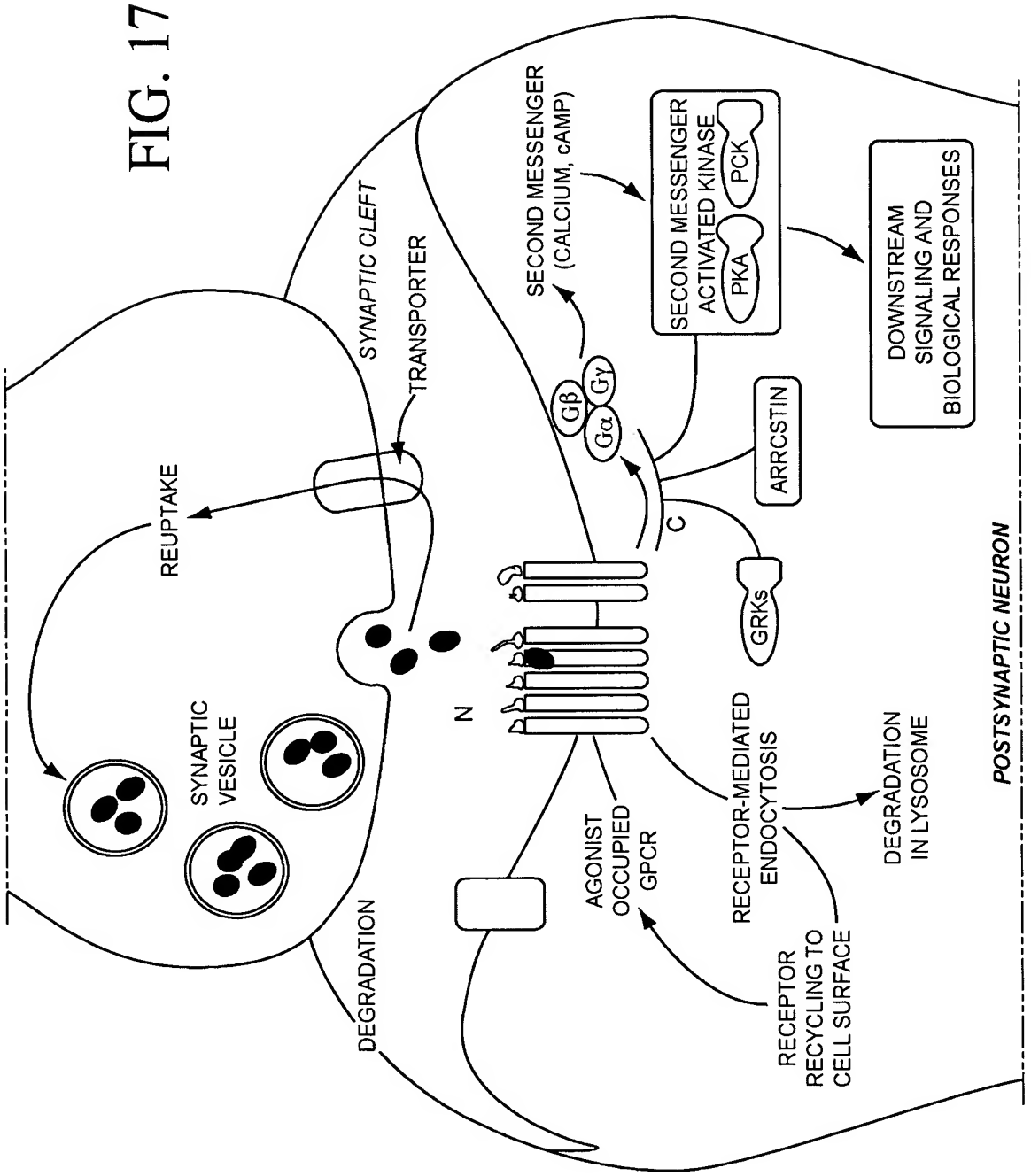
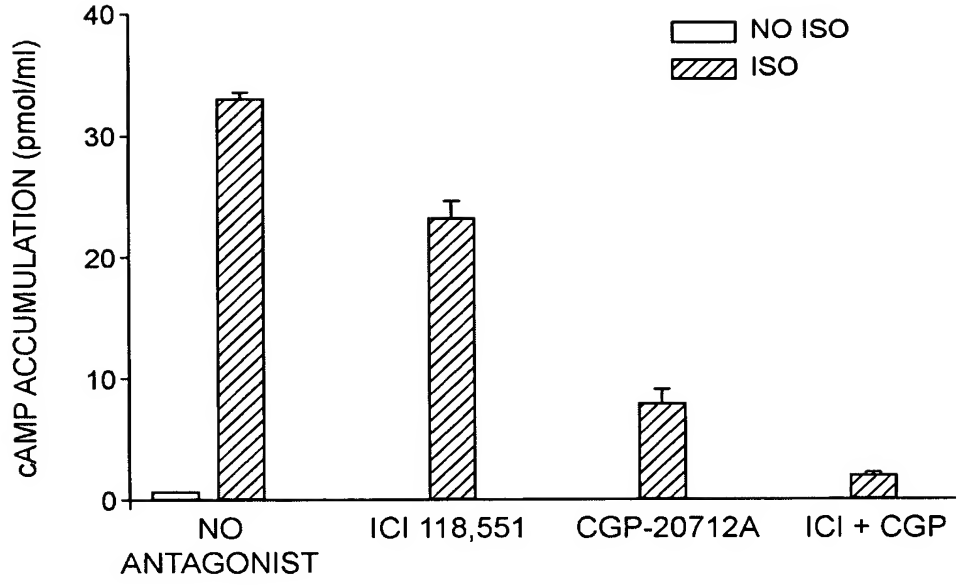

REUPTAKE
SYNAPTIC VESICLE
DEGRADATION
SYNAPTIC CLEFT
TRANSPORTER
N
C
AGONIST OCCUPIED GPCR
RECEPTOR RECYCLING TO CELL SURFACE
RECEPTOR-MEDIATED ENDOCYTOSIS
DEGRADATION IN LYSOSOME
GRKs
ARRCSTIN
Gβ
Gγ
Gα
SECOND MESSENGER (CALCIUM, cAMP)
SECOND MESSENGER ACTIVATED KINASE
PKA
PCK
DOWNSTREAM SIGNALING AND BIOLOGICAL RESPONSES
POSTSYNAPTIC NEURON

FIG. 18


cAMP ACCUMULATION (pmol/ml)
40
30
20
10
0
NO ISO
ISO
NO ANTAGONIST
ICI 118,551
CGP-20712A
ICI + CGP

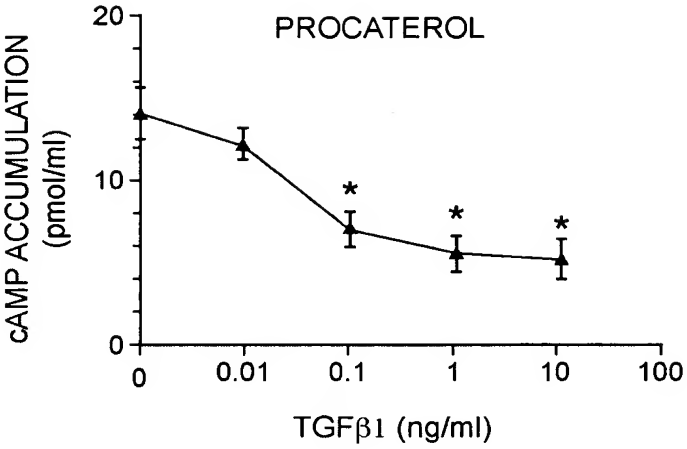


FIG. 19A

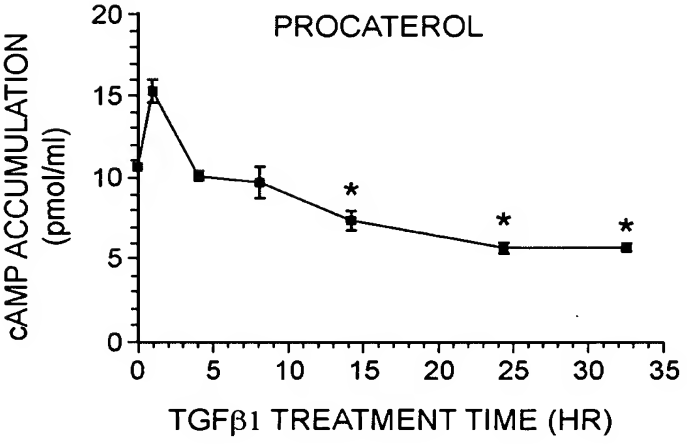


FIG. 19B

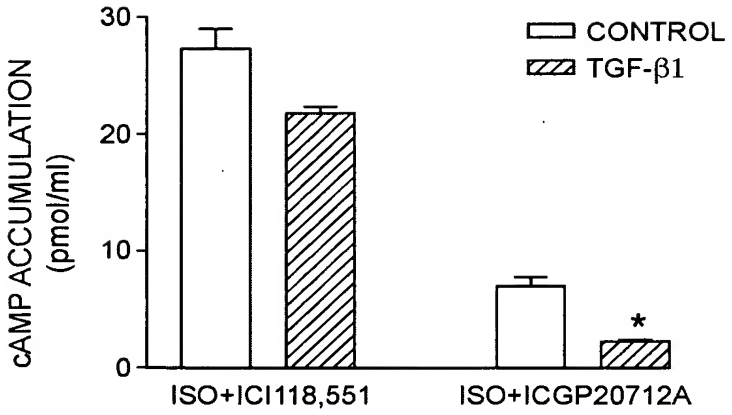


FIG. 19C

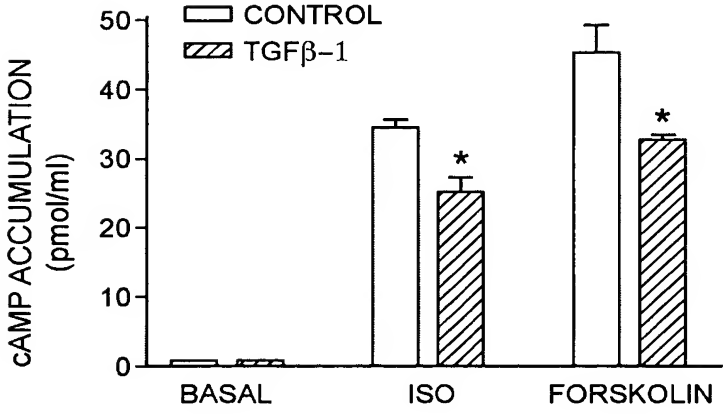


FIG. 19D

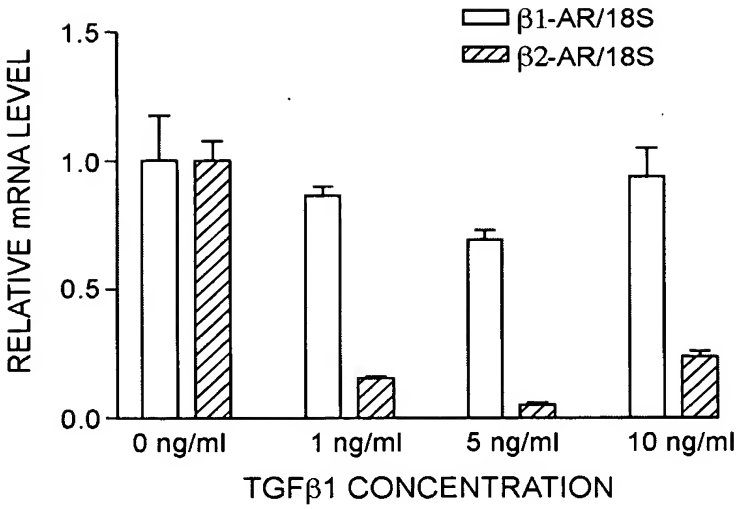


FIG. 20A

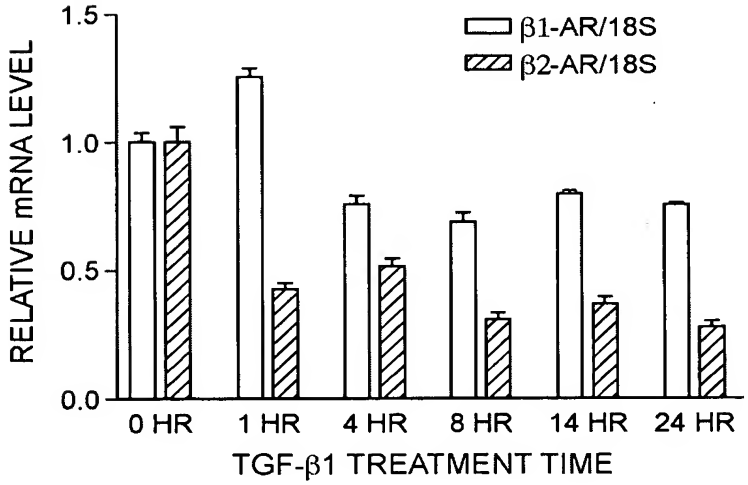


FIG. 20B

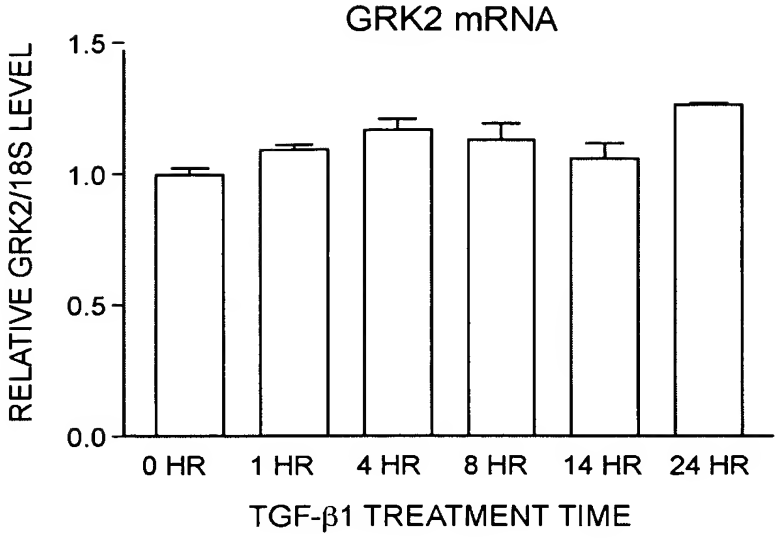


FIG. 21A

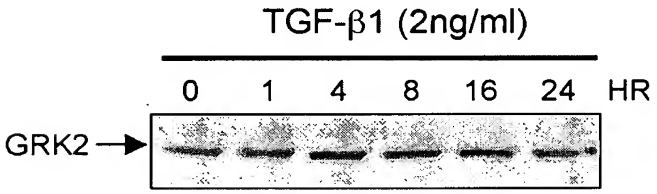


FIG. 21B

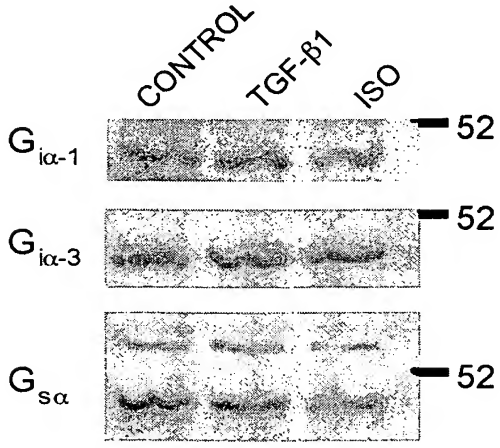


FIG. 21C

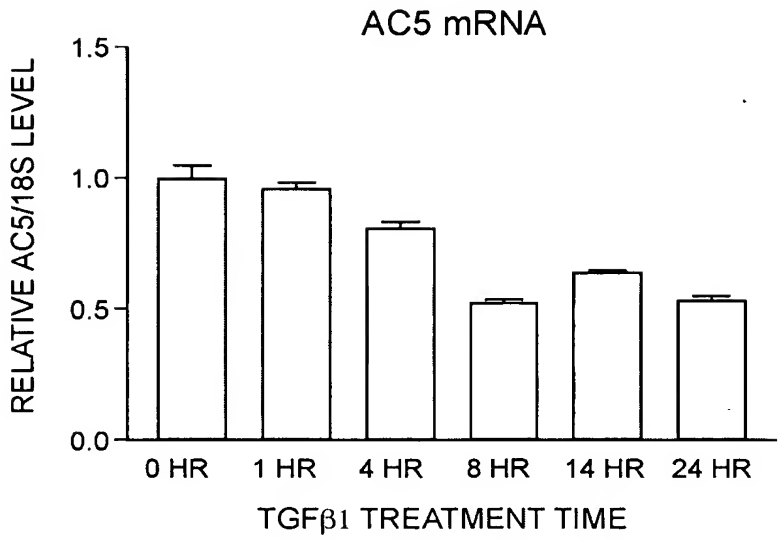


FIG. 21D

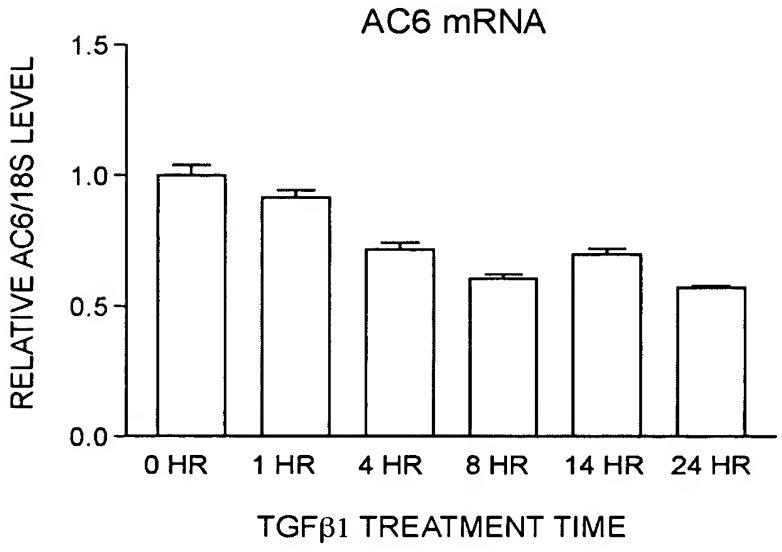


FIG. 21E

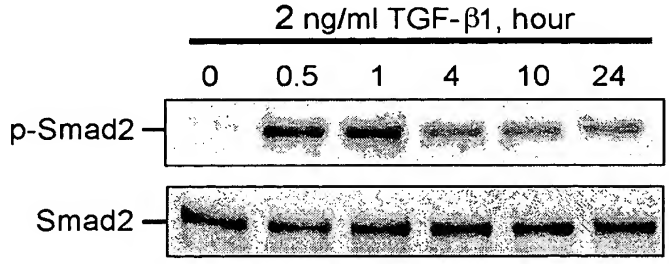


FIG. 22A

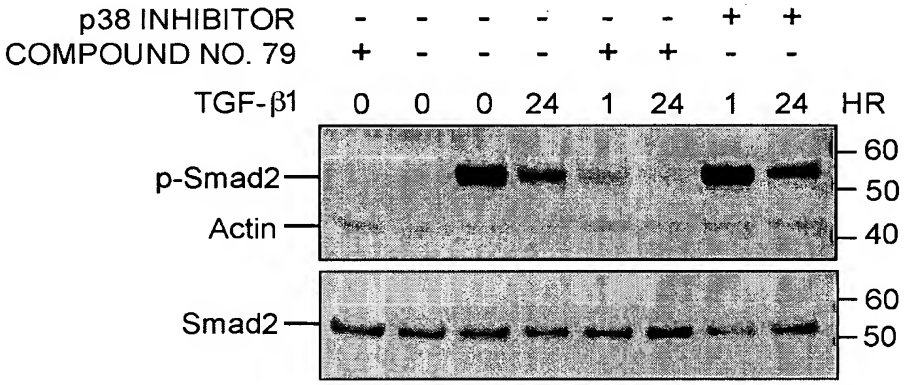


FIG. 22B

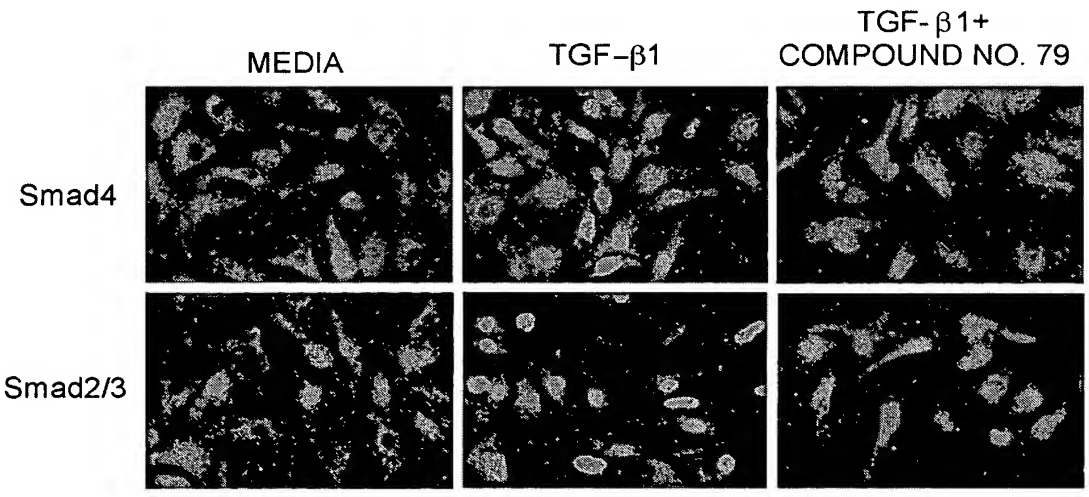


FIG. 22C

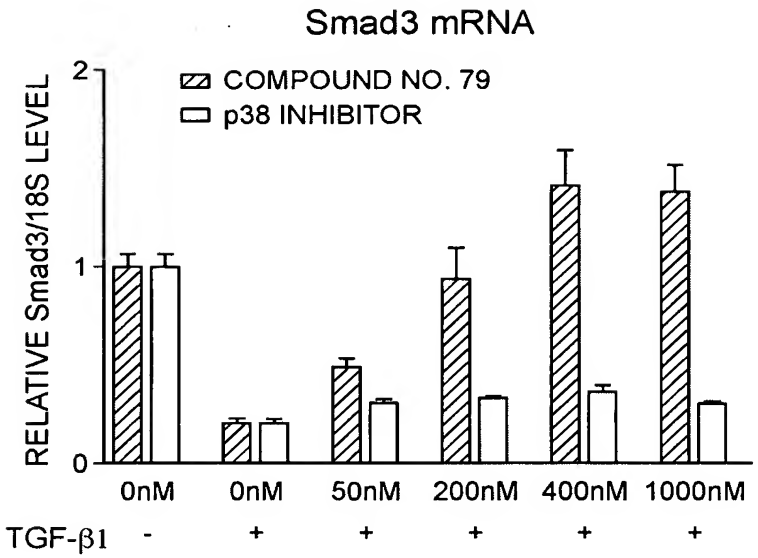


FIG. 23A

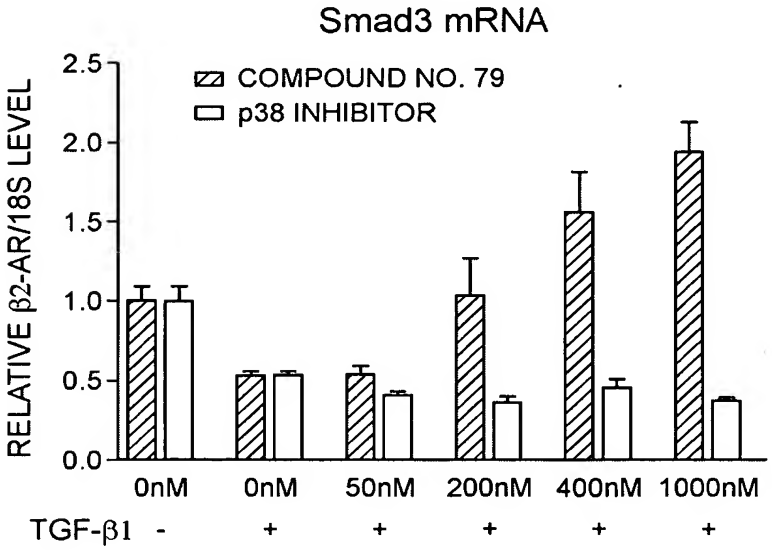


FIG. 23B

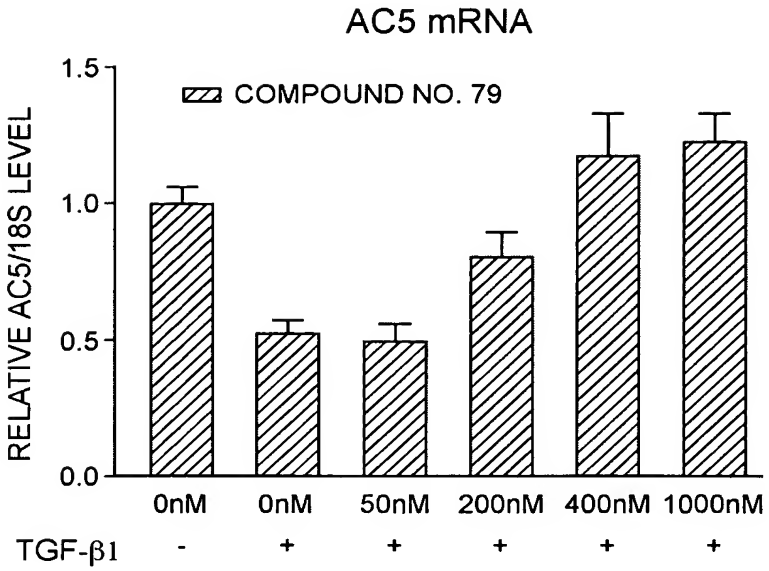


FIG. 23C

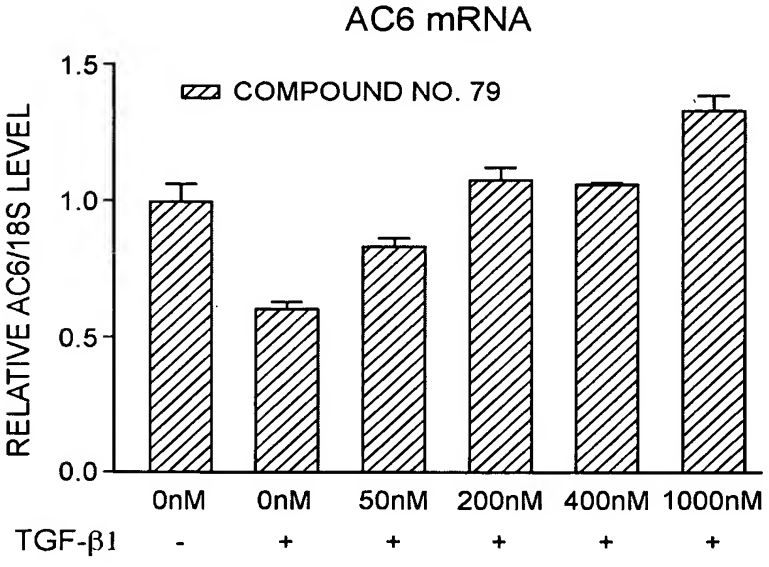


FIG. 23D

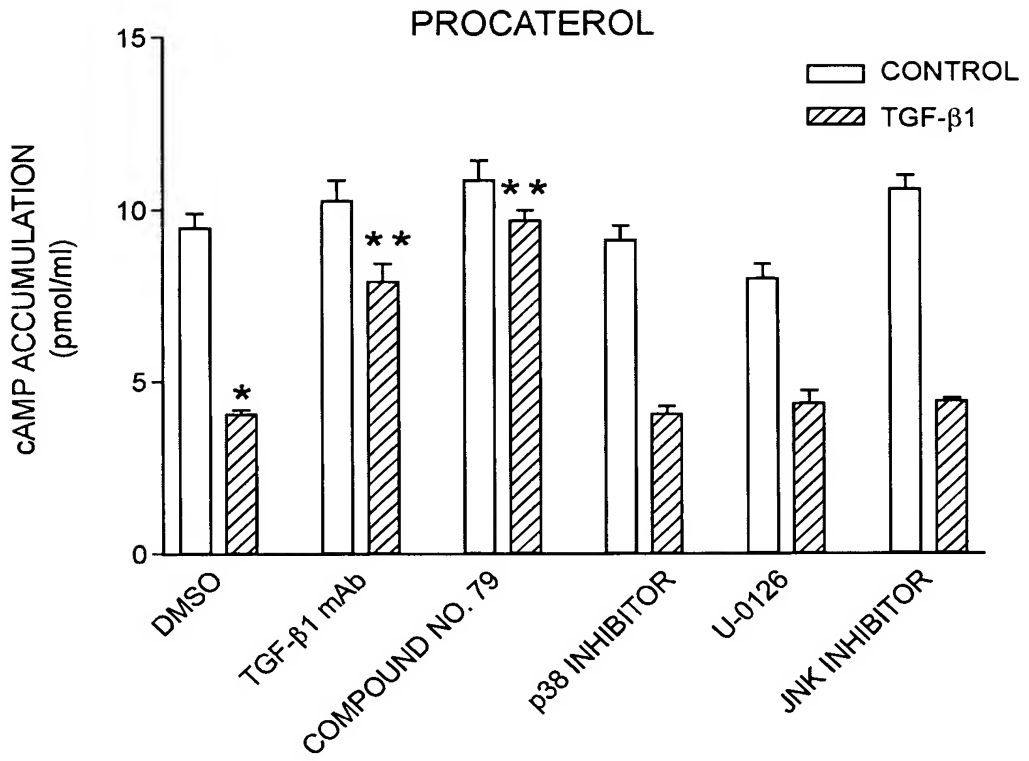


FIG. 24A

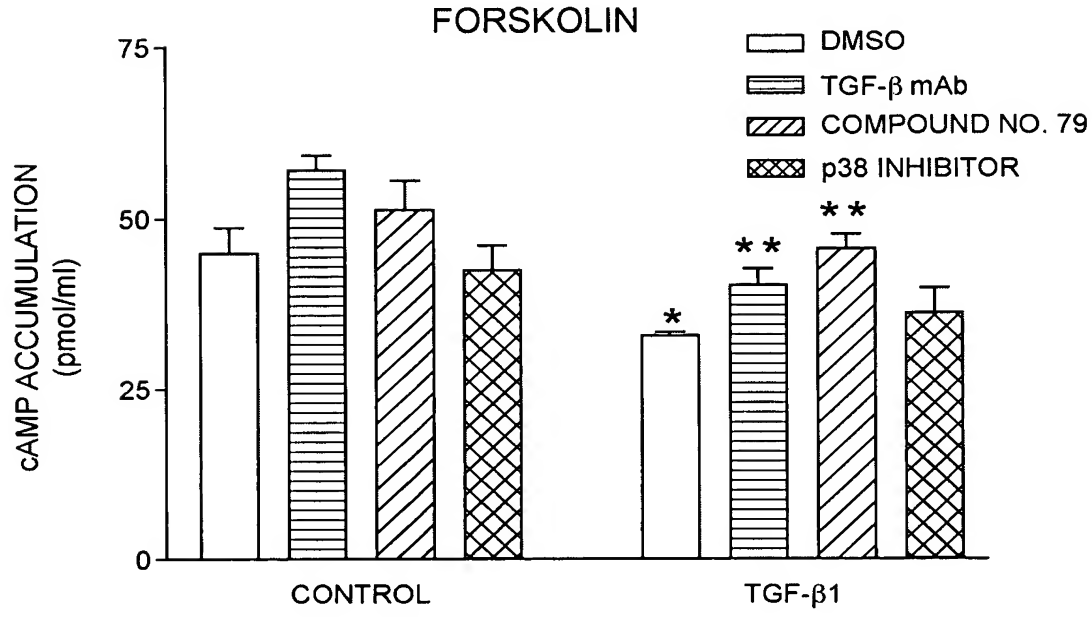


FIG. 24B

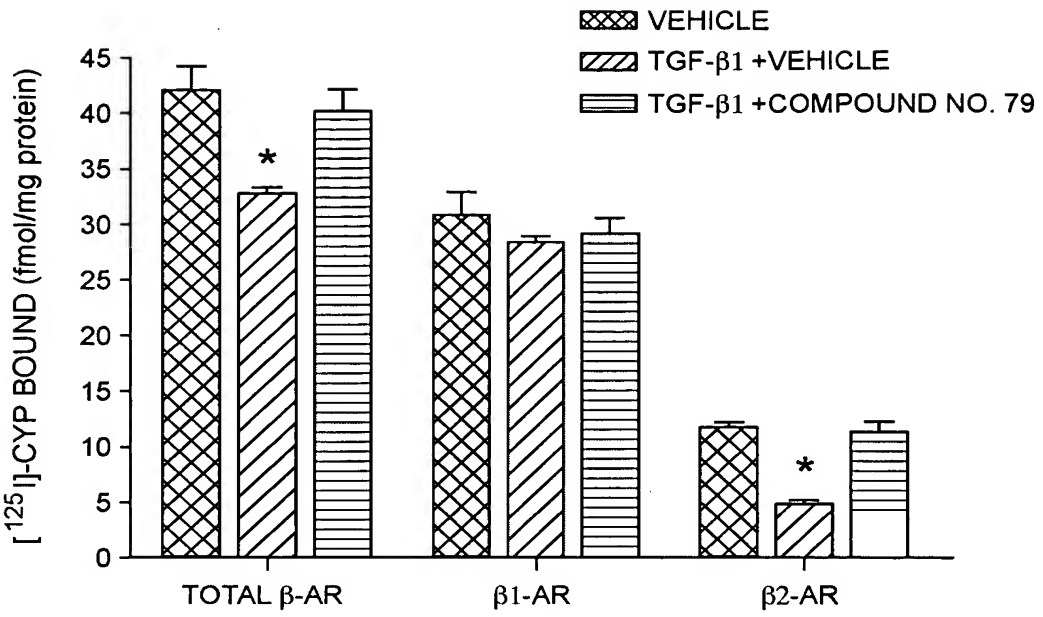


FIG. 25

ALTERATION OF β-AR BINDING SITES BY TGF-β1 AND COMPOUND NO. 79 IN CARDIOMYOCYTES